A dynamic interplay of enhancer elements regulates Klf4 expression in naive pluripotency.

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Public Summary:
Transcription factor (TF)-directed enhanceosome assembly constitutes a fundamental regulatory mechanism driving spatiotemporal gene expression programs during animal development. Despite decades of study, we know little about the dynamics or order of events animating TF assembly at cis-regulatory elements in living cells and the long-range molecular "dialog" between enhancers and promoters. Here, combining genetic, genomic, and imaging approaches, we characterize a complex long-range enhancer cluster governing Kruppel-like factor 4 (Klf4) expression in naive pluripotency. Genome editing by CRISPR/Cas9 revealed that OCT4 and SOX2 safeguard an accessible chromatin neighborhood to assist the binding of other TFs/cofactors to the enhancer. Single-molecule live-cell imaging uncovered that two naive pluripotency TFs, STAT3 and ESRRB, interrogate chromatin in a highly dynamic manner, in which SOX2 promotes ESRRB target search and chromatin-binding dynamics through a direct protein-tethering mechanism. Together, our results support a highly dynamic yet intrinsically ordered enhanceosome assembly to maintain the finely balanced transcription program underlying naive pluripotency.

Scientific Abstract:
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